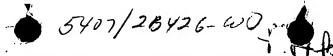


PCT



WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau

455 N 10/087,19

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:

A23K 1/16, 1/18, A61K 31/205

A1

(11) International Publication Number:

WO 98/24328

(43

US

US

(43) International Publication Date:

11 June 1998 (11.06.98)

(21) International Application Number:

PCT/US97/22215

(22) International Filing Date:

3 December 1997 (03.12.97)

(30) Pri rity Data:

759,765 844,918 3 December 1996 (03.12.96)

22 April 1997 (22.04.97)

(63) Related by Continuation (CON) or Continuation-in-Part

(CIP) to Earlier Application US

08/844,918 (CON)

Filed on

22 April 1997 (22.04.97)

(71) Applicant (for all designated States except US): KANSAS STATE UNIVERSITY RESEARCH FOUNDATION [US/US]; 1500 Hayes Drive, Manhattan, KS 66502-5068 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): NELSSEN, Jim, L. [US/US]; 7234 Tuttle Creek Boulevard, Manhattan, KS 66503 (US). GOODBAND, Robert, D. [US/US]; 7661 Fairview Church Road, Manhattan, KS 66503 (US). TOKACH, Michael, D. [US/US]; 1221 2600 Avenue, Abilene, KS 67410 (US). OWEN, Kevin, Q. [US/US]; 3325

Effingham, Manhattan, KS 66503 (US). MUSSER, Robert, E. [US/US]; 707 Pine Street, Wamero, KS 66547 (US).

(74) Agents: LEWEN, Bert, J. et al.; Darby & Darby P.C., 805 Third Avenue, New York, NY 10022 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: CARNITINE-SUPPLEMENTED DIETS FOR GESTATING AND LACTATING SWINE

(57) Abstract

The present invention relates to a method of feeding carnitine supplemented diets to sows during the period of gestation or during both gestation and lactation periods. The method enhances pork productivity by increasing litter and pig birth and weaning weights, reducing the number of stillborn pigs and increasing the number of pigs born alive in the subsequent reproductive cycle. Sow diets of this invention include carnitine, such as L-carnitine or L-carnitine salts. Carnitine is generally added to the swine feed formulation in the amount of from about 5 to about 5,000 ppm.

${\it FOR\ THE\ PURPOSES\ OF\ INFORMATION\ ONLY}$

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
ΑÜ	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
BJ	Benin	IE	Ireland	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	Iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Viet Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
СН	Switzerland	KG	Kyrgyzstan	NO	Norway	zw	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland .		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan -		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION International Bureau



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:

A23K 1/16, 1/18, A61K 31/205

(11) International Publication Number:

WO 98/24328

(43) International Publication Date:

11 June 1998 (11.06.98)

(21) International Application Number:

PCT/US97/22215

A1

(22) International Filing Date:

3 December 1997 (03.12.97)

(30) Priority Data:

759,765 844,918

3 December 1996 (03.12.96) US

22 April 1997 (22.04.97)

US

(71) Applicant (for all designated States except US): KANSAS STATE UNIVERSITY RESEARCH FOUNDATION [US/US]; 1500 Hayes Drive, Manhattan, KS 66502-5068

(72) Inventors; and

- (75) Inventors/Applicants (for US only): NELSSEN, Jim, L. [US/US]; 7234 Tuttle Creek Boulevard, Manhattan, KS 66503 (US). GOODBAND, Robert, D. [US/US]; 7661 Fairview Church Road, Manhattan, KS 66503 (US). TOKACH, Michael, D. [US/US]; 1221 2600 Avenue, Abilene, KS 67410 (US). OWEN, Kevin, Q. [US/US]; 3325 Effingham, Manhattan, KS 66503 (US). MUSSER, Robert, E. [US/US]; 707 Pine Street, Wamero, KS 66547 (US).
- (74) Agents: LEWEN, Bert, J. et al.; Darby & Darby P.C., 805 Third Avenue, New York, NY 10022 (US).

(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published

With international search report.

Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: CARNITINE-SUPPLEMENTED DIETS FOR GESTATING AND LACTATING SWINE

(57) Abstract

The present invention relates to a method of feeding carnitine supplemented diets to sows during the period of gestation or during both gestation and lactation periods. The method enhances pork productivity by increasing litter and pig birth and weaning weights, reducing the number of stillborn pigs and increasing the number of pigs born alive in the subsequent reproductive cycle. Sow diets of this invention include carnitine, such as L-carnitine or L-carnitine salts. Carnitine is generally added to the swine feed formulation in the amount of from about 5 to about 5,000 ppm.

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
AM	Armenia	FI	Finland	LT	Lithuania	SK	Slovakia
AT	Austria	FR	France	LU	Luxembourg	SN	Senegal
AU	Australia	GA	Gabon	LV	Latvia	SZ	Swaziland
AZ	Azerbaijan	GB	United Kingdom	MC	Monaco	TD	Chad
BA	Bosnia and Herzegovina	GE	Georgia	MD	Republic of Moldova	TG	Togo
BB	Barbados	GH	Ghana	MG	Madagascar	TJ	Tajikistan
BE	Belgium	GN	Guinea	MK	The former Yugoslav	TM	Turkmenistan
BF	Burkina Faso	GR	Greece		Republic of Macedonia	TR	Turkey
BG	Bulgaria	HU	Hungary	ML	Mali	TT	Trinidad and Tobago
RJ	Benin	IE	fretand	MN	Mongolia	UA	Ukraine
BR	Brazil	IL	Israel	MR	Mauritania	UG	Uganda
BY	Belarus	IS	iceland	MW	Malawi	US	United States of America
CA	Canada	IT	Italy	MX	Mexico	UZ	Uzbekistan
CF	Central African Republic	JP	Japan	NE	Niger	VN	Vict Nam
CG	Congo	KE	Kenya	NL	Netherlands	YU	Yugoslavia
CH	Switzerland	KG	Kyrgyzstan	NO	Norway	zw	Zimbabwe
CI	Côte d'Ivoire	KP	Democratic People's	NZ	New Zealand		
CM	Cameroon		Republic of Korea	PL	Poland		
CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	u	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore .		

10

15

20

lean to fat ratio of pigs. Its beneficial effects of increasing carcass leanness and improving the lean to fat ratio were also shown in fish (U.S. Pat. No: 5,030,657). In addition, carnitine has been shown to improve the hatchability of eggs when fed to laying hens (U.S. Patent No. 5,362,753).

Carnitine is synthesized in the body from two essential amino acids, protein bound lysine and methionine. The level of enzyme involved in the synthesis of carnitine is extremely low in newborn piglets (Coffey et al., Carnitine Status and Lipid Utilization in Neonatal Piglets Fed Diets Low in Carnitine, J. Nutr. 121:1047-53; 1991). The newborn piglet must quickly switch from carbohydrate transplacental nourishment to a high-fat milk based diet. Thus, during the suckling period, the neonate must quickly develop the capacity to oxidize fatty acids and ketone bodies as fuel alternatives to carbohydrates. Given the role of carnitine in the fatty acid metabolism, its availability to newborns in adequate amounts is essential (Borum, P.R., Variation in Tissue Carnitine Concentration with Age and Sex in the Rat, Biochem J. 176:677; 1978).

The primary source of carnitine in neonatal tissue, at least 2-3 days post partum, is milk (Robles-Valdez et al., Maternal Fetal Carnitine Relationships and Neonatal Ketosis in the Rat, J. Biol. Chem. 251:6007; 1976). The presence of carnitine in the milk should enhance the piglets' ability to utilize milk fat. Coffey et al. compared lipid utilization by pigs nursing from their sow with lipid utilization by pigs fed a milk replacer with or without added carnitine and found that nursing pigs were heavier than pigs fed milk replacer. However, pigs fed the milk replacer with added carnitine grew faster (day 7 to 21) than those fed the milk replacer without carnitine. Carnitine supplementation did not affect lipid or glucose status of the pig.

Other researchers have described the effect of supplemented carnitine on milk production and fatty acid metabolism. Erfle et al. (Effect of Infusion of Carnitine and Glucose on Blood Glucose, Ketones, and Free fatty Acids of Ketotic Cows, J. Dairy Sci. 54:673-80; 1971) infused carnitine into ketotic lactating dairy cows and found improved fatty acid oxidation.

WQ 98/24328 PCT/US97/22215

5

10 CARNITINE-SUPPLEMENTED DIETS FOR GESTATING AND LACTATING SWINE

This application is a continuation in part application of U.S. Application No: 08/844,918 filed April 22, 1997, which is a continuation of U.S. Application Ser. No: 08/759,765 filed December 3, 1996. Both applications are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

The present invention is in the general field of swine farming and relates to feeding carnitine-supplemented diets to swine during the period of gestation or during the periods of both gestation and lactation to increase pork productivity by, for example, increasing litter and pig weights at birth and at the time of weaning and by increasing the number of pigs born alive in the subsequent reproductive cycle (i.e., the cycle following the cycle of carnitine supplementation). Swine diets of this invention include carnitine, such as L-carnitine or L-carnitine salts, present in the amount effective to increase the litter and pig birth and weaning weights.

BACKGROUND OF THE INVENTION

Carnitine is a naturally occurring B vitamin-like compound found in humans and other mammals. Carnitine has many functions, but its primarily role is in the transport of fatty acids into the mitochondria. Previous research (U.S. Patent Nos. 5,124,357 and 5,192,804) has shown that carnitine supplementation of diets increases the

WO 98/24328 PCT/US97/22215

3

As noted above, the availability of carnitine in the diet of newborn pigs is essential for efficient transition to a high-fat milk diet. However, methods for supplementing the milk diet of nursing pigs with carnitine are presently unavailable. Use of milk replacer containing carnitine as suggested for cows would not be practicable on a large commercial scale. More importantly, milk replacers do not contain all other essential components of the swine milk. There is therefore a need in the art for alternative ways for improving the performance of newborn pigs and particularly for increasing pig and litter birth and weaning weights.

Previous research has suggested that feeding L-carnitine supplemented diets to sows during the last 10 days of gestation and continuing during the entire period of lactation has certain beneficial effects on litter performance. Fremaut, D. et al., Do Lactating Sows Benefit from L-Carnitine Supplementation, Varkensbedrijf, June 1993: 20-23.

Applicants have now surprisingly discovered that feeding sows a diet containing L-carnitine only during the period of gestation substantially increases litter and pig performance both at birth and at weaning. The litter and pig performance was also improved when sow diets were supplemented with carnitine during both gestation and lactation periods. However, feeding carnitine to sows substantially only during lactation was not found particularly beneficial.

20

15

SUMMARY OF THE INVENTION

The present invention relates to feeding carnitine-supplemented diets to swine during the period of gestation only, or during both gestation and lactation, to increase litter and pig performance and increase pork productivity.

Accordingly, one aspect of the present invention is a method of feeding carnitine-supplemented diets to sows during the period of gestation to increase litter and pig performance at birth and/or at weaning.

10

20

25

egeragina es

Another aspect of the present invention is a method of feeding carnitinesupplemented diets to sows during the periods of both gestation and lactation to increase litter and pig performance at birth and/or at weaning.

Yet another aspect of the present invention is a method of feeding carnitinesupplemented diets to sows during the period of gestation only or during both gestation and lactation to reduce the number of stillborn pigs.

Still another aspect of the present invention is a method of increasing pork productivity by increasing the number of pigs born alive in the subsequent, second reproductive cycle by supplementing a swine diet with carnitine in the first reproductive cycle during gestation only or during both gestation and lactation.

Still another aspect of the present invention is a method of increasing pork productivity by supplementing a swine diet with carnitine and feeding the supplemented diet to swine during gestation only or during both gestation and lactation.

15 <u>DETAILED DESCRIPTION OF THE INVENTION</u>

All patents, patent applications and literature references cited in this specification are hereby incorporated by reference in their entirety.

The present invention relates to feeding carnitine-supplemented diets to swine during the period of gestation only, or during both gestation and lactation, to improve litter and pig performance. Generally, feeding L-carnitine supplemented diets to sows improves pig and litter weights at birth and/or weaning and increases the number of pigs born alive in the subsequent reproductive cycle. The invention also relates to increasing pork productivity by supplementing a swine diet with carnitine and feeding the supplemented diet to swine during gestation only or during both gestation and lactation.

In the practice of this invention, the female swine diet can be supplemented with carnitine from approximately mating. Carnitine can be fed throughout the period of gestation (i.e., from approximately mating to approximately parturition) or for a portion thereof. Carnitine can also be fed from mating and throughout the period of lactation (i.e., from approximately parturition until offspring is weaned or lactation is terminated by

10

15

20

decision of the herdsperson) or for a portion of lactation period. Most preferably, for the efficient use of carnitine, carnitine is supplemented throughout the period of gestation or a portion thereof, *i.e.*, not during lactation.

L-carnitine supplemented diets can be fed according to the present invention for a portion of the gestation or lactation period. In one preferred embodiment, the diet is fed five days after breeding until farrowing, i.e., 109 days out of 114 days of gestation. The diet can also be fed for a shorter period during gestation, for example for at least 5 days, and preferably for at least 10 days, during the first 90 days of gestation. In another preferred embodiment, carnitine is supplemented for at least 5 days, and preferably for at least 10 days, during the first 60 days of gestation.

To increase litter performance at birth and/or weaning, the diet is fed during gestation only or during both lactation and gestation. It has been found that feeding sows L-carnitine supplemented diets during the period of lactation only does not significantly improve litter performance in comparison to the control.

The feed formulation of the invention comprises carnitine. The supplemental carnitine can be any isomer of carnitine, preferably L-carnitine. Also suitable for formulation of the diet of the present invention are salts of carnitine, such as acetyl carnitine, and di-carnitine-tartrate. These materials may be encapsulated or protected.

The carnitine is present in the feed formulation of the invention in an amount effective to achieve the desired improvement of litter and pig performance, such as an increase in pig and litter birth or weaning weights or a reduction of the number of stillborn pigs or an increase in number of pigs born alive in the subsequent reproductive cycle. This improvement can be of any level above the litter and pig performance of swine fed a diet without carnitine, as even the small differences in birth or weaning weights have significant effect on meat productivity. For example, the methods of the present invention decrease fixed investment costs and production costs since the period from the pig birth to the meat market is shorter then when swine are fed conventional diets.

Generally, the feed formulation for use in the invention contains from about 5 to about 5,000 ppm of carnitine, preferably from about 5 to about 200 ppm. Given the detailed guidance of the present specification, it is believed that it is within the level of one of ordinary skill to test a range of carnitine concentrations using a trial feed in order to optimize the concentration for the particular breed and stage of development being fed. Generally, a gestating swine is fed from approximately 9 to approximately 14,000 mg carnitine per day, more preferably from approximately 9 to approximately 550 mg carnitine per day. A lactating swine is fed from approximately 20 to approximately 34,000 mg carnitine per day, more preferably from approximately 20 to approximately 1,400 mg carnitine per day.

The base diet of the present invention can be any typical swine diet known in the art, including those specially formulated for gestating or lactating swine. For example, a typical diet will include a selection of the ingredients described below.

Extensive guidance in formulating diets for the feeding of swine can be found in "Nutrient Requirements of Swine", Nutrient Requirements of Domestic Animals, Number 3, 9th rev. ed. (National Academy of Science, Washington, D.C. (1988)).

In the United States, most swine are fed a diet consisting of about 97% milo or corn in combination with soybean, the remaining 3% consisting of carriers combined with one or more inorganic elements, vitamins, or antimicrobial compounds.

20 For example, a standard diet may contain 79.5% corn; 17.4% soybean meal; 0.9% defluorinated phosphate; 0.65% limestone meal (35% Ca); 0.25% sodium chloride; 0.25% vitamin premix; 0.25% trace element premix; and 0.25% antimicrobial premix. Oats, sorghum and synthetic amino acids are sometimes added. In Europe, corn and soybean meal are generally not as available nor as cost effective as beans, peas, barley, wheat, rape seed meal, cassava (tapioca), molasses, fish, bone, and meat meal. These are acceptable although not preferred amino acid sources.

In formulating the diets for gestating or lactating swine, a person of skill in the art can use the general knowledge in the art. For example, the Nutrient Requirements of Swine can be consulted to determine the amino acids, mineral elements, vitamins, and WO 98/24328 PCT/US97/22215

7

other dietary requirements for swine as a function of weight. The diet can contain between 5 and 30% by weight crude protein and be formulated for the specific use as a gestation or a lactation diet. For example, a gestating swine diet may contain from about 100 to about 400 g/hd/day of crude protein, from about 7 to about 14 g/hd/day of lysine, from about 12 to about 18 g/hd/day of calcium and from about 10 to about 16 g/hd/day of phosphorus. An exemplary lactating swine diet may contain 600 to about 1800 g/hd/day of crude protein, from about 30 to about 70 g/hd/day of lysine, from about 35 to about 55 g/hd/day of calcium and from about 30 to about 50 g/hd/day of phosphorus.

A further example of recommended daily nutrient levels during gestation and lactation expressed in grams per head per day (g/hd/day), except where noted otherwise, is shown in Table 1.

15

- kropádoá

TABLE 1

COMPONENT **GESTATION** LACTATION Crude Protein 250 899 Lysine 11 44 Tryptophan 2.5 11 Threonine 8 32 **Minerals** Calcium 16 48 Phosphorus 14.5 43 Salt 9 27 Copper, mg 30 90 Iodine, mg .54 1.6 Iron, mg 300 900 Manganese, mg 72 216 Selenium, mg $.18^{2}$.54b Zinc, mg 300 900

25

20

30

	Vitamins		
5	Vitamin A, IU Vitamin D, IU Vitamin E, IU Vitamin K, mg Riboflavin, mg Niacin, mg d-Pantothenic	20,000 3,000 80 8 15 90	60,000 9,000 240 24 45 270
10	Acid, mg Vitamin B ₁₂ , mg Folic Acid, mg Biotin, mg Choline, mg	52 .06 3 .4 1,000	156 .18 9 1.2 3,000

e menadione sodium bisulfite (MSB) or equivalent

20

As shown in Table 1, feed formulations for gestating swine are different from feed formulations for lactating swine. Generally, a requirement for protein, lysine, tryptophan and threonine is from about 3.5 to about 4 times higher for lactating swine.

Other feed components necessary for both types of feeds may be, for example, in the following ranges expressed in pounds of a component per 2000 pounds of 25 feed:

30

35

TABLE 2

COMPONENT	GESTATION FEED	LACTATION FEED
Milo or Corn, lb	1,533-1,684	1,359-1,568
Soybean Meal, lb (46.5%)	235-379	343-557

a legal addition if fed 4lb/hd/day

b assumes at least 12lb/day feed intake of a diet containing .80% lysine

Monocalcium Phosphate, lb	37-46	41-45
Limestone, lb	20	19-20
Salt, lb	10	10
Sow Add Pack, lb	5	5
Vitamin Premix, Ib	5	5
Trace Mineral Premix, lb	3	3
Selenium Premix, lb	1	1

5

Suitable swine to be fed the diet of the present invention include but are not limited to all standard breeds of swine such as large white breeds and swine derived from specific breeding companies (PIC, Newsham, Dekalb and others).

The feed schedule and feed rates used with the present method can be any standard schedule and rate used in the art. Generally, gestating swine are fed from about 4 to about 6 pounds of the diet per day, and preferably from about 4 to about 5 pounds per day. Lactating swine are generally fed from about 9 to about 15 pounds of the diet per day, and preferably from about 13 to about 14 pounds per day. Generally, the feed is administered from 1 to 2 times a day for gestating swine and from 1 to 2 and up to 4 times a day for lactating swine.

The following non-limiting example is representative of the present invention.

25 EXAMPLE 1: Effect of L-carnitine Fed During Gestation, Lactation or Both on Sow and Litter Performance

A total of 307 sows (PIC Line C-15 x 326) were used to determine the effect of feeding 50 ppm L-carnitine on the sow and litter performance. Sows were randomly assigned to either control or test dietary treatments. The three test treatments

were designated as follows: (i) control/carnitine (in which carnitine was supplemented only during the period of lactation); (ii) carnitine/control (in which carnitine was supplemented only during the period of gestation) and (iii) carnitine/carnitine (in which carnitine was supplemented during the periods of both gestation and lactation).

A gestation diet was formulated to contain nutrients in excess of NRC (1988) estimates, and included 79.51% milo; 15.22% soybean meal (46.5 % CP); 2.51% monocalcium phosphate; 1.11% limestone; 0.5% sodium chloride; 0.25 % sow premix; 0.25% vitamin premix; and 0.15% trace element premix. This diet contained 0.65% total lysine, 0.95% Ca and 0.85% P. Experimental gestation diet contained 50 ppm L-carnitine. Sows were fed 4 lb of diet/day once a day until farrowing. Sows were weighed and last rib fat debt was recorded at day 110 of gestation. At farrowing, a number of pigs born live, stillborns, and mummies were recorded. Individual pig weight and litter weight were also recorded. Within 48 hours from farrowing, litters were equalized within dietary treatment.

A lactation diet was formulated to contain nutrients in excess of NRC (1988) estimates, and included 62.91% milo; 28.41% soybean meal (46.5 % CP); 4% soybean oil; 2.33% monocalcium phosphate; 1.12% limestone; 0.5% sodium chloride; 0.25 % sow premix; 0.25% vitamin premix; 0.15% trace element premix; 0.05% vitamin E and 0.02% DL-Methionine. This diet contained 1.0% total lysine, 0.95% Ca and 0.85% P. Experimental lactation diet contained 50 ppm L-carnitine. The sows were allowed ad libitum access to feed. Feed intake was measured weekly. Pigs were weighed at weaning to determine pig and litter weight. Sows were ultrasonically scanned for last rib fat debt at weaning.

Sows were bled at day 10, 60, 90 and 110 of gestation and at weaning.

25 Plasma samples were analyzed for concentration of free and total carnitine, insulin, and insulin-like growth factor I (IGF-I).

The data were analyzed by analysis of variance using GLM procedure of SAS (1988).

The results are represented in Table 3.

Feeding L-carnitine supplemented diets only during gestation increased both pig (P< 0.01) and litter (P< 0.03) birth weights. It also increased pig (P< 0.01) and litter (P< 0.07) weight at weaning, and pig (P< 0.03) and litter (P< 0.12) weight gain.

The results also showed that the number of stillborn pigs per litter

decreased when sows were fed carnitine-supplemented diets during gestation only (.49 vs

.76 stillborn pigs/litter; P < .02).

With respect to sow performance, feeding L-carnitine during gestation only resulted in heavier sows at weaning compared to control sows (511 lb vs. 493; P < 0.01).

Feeding carnitine during both gestation and lactation also had beneficial effects. For example, sow weight at weaning was 524 lb for sows feed carnitine during birth periods and 493 lb for control sows. However, referring to Table 3, no differences were observed in either sow or litter performance as a result of feeding carnitine during the period of lactation only.

With respect to sow plasma analysis, L-carnitine supplementation tended to increase insulin levels in the plasma of sows at days 10 and 60 of gestation (P < 0.07), and IGF-I concentration tended to increase at gestation days 60 and 90. Since insulin and IGF-I may increase secondary muscle fiber in the fetal pig and IGF-I may play a role in myogenic differentiation and proliferation, these results suggest that feeding carnitine can have an overall beneficial effect on pork productivity.

The effect of carnitine on subsequent reproductive performance was also measured. Sows fed diets described above were continued to be monitored during the subsequent, *i.e.*, second cycle of reproduction. The sow diets were not supplemented with carnitine during the second cycle of reproduction to determine if carnitine had any residual effect. The total number of pigs born and the number of pigs born alive were determined. Referring to Table 5, feeding carnitine in the first reproductive cycle increased the total number of born pigs and the number of pigs born alive in the second reproductive cycle.

ABLE 3

		Dietary Treatment	reatment			Pro	Probability (P <	
Gestation: Item Lactation:	Control Control	Control Carnitine	Carnitine Control	Camitine Camitine	SEM	Gest.	Lact.	Gest. x Lact.
No. sows	75	75	86	58				
Parity	3.72	3.82	3.64	3.77	. 13	.63	.43	.92
Lactation length, days	15.7	15.9	15.3	15.7	.16	.15	.30	.62
Pigs equalized by day 2	86.6	10.09	10.20	10.01	.32	.85	.91	19.
Litter birth weight, 1b	31.50	32.73	34.46	34.49	86.	.03	.55	.57
Pig birth weight, 1b	3.22	3.32	3.45	3.53	90.	10.	.17	.81
Pigs weaned per litter	8.91	8.89	9.02	9.00	.31	.76	96.	66.
Survivability, %	89.57	86.08	86.87	90.45	1.84	69'	86.	01.
Litter weight at weaning, 1b	90.71	91.91	69.76	99.03	3.41	.07	.75	66.
Pig wean weight, 1b	10.33	10.38	10.94	10.99	.18	.01	.79	.99
Litter weight gain, 1b	58.69	58.59	62.83	64.25	2.71	.12	.84	.81
Pig weight gain, 1b	7.08	7.11	7.52	7.45	.15	.03	.91	.76
Average daily feed intake, 1b								
wk 1	11.70	11.55	11.52	11.88	.19	.73	.64	.28
wk 2	14.35	14.41	14.70	14.87	.21	11.	49.	.28
overall	13.22	13.01	13.16	13.58	.17	.20	.63	.12
*Analyzed with pigs per litter of	gs per litter on day 2 as the covariate.	e covariate.						

ABLE 4

Effects of L-Carnitine on Subsequent Reproductive Performance

		Dietary Treatment	reatment			Pr	Probability (P<)	v
Gestation: Item Lactation:	Control Control	Control Carnitine	Carnitine Control	Carnitine Carnitine	SEM	Gest.	Lact.	Gest. x Lact.
No. sows	47	44	55	37				
No. sows removed	28	31	31	21				
Days to estrus	5.28	5.82	6.11	5.37	.38	28	8	12
Farrowing rate, %	96.1	96.3	86.5	93.2	.05	22	2	2
Number total born	11.24	12.26	11.97	12.85	.40	.21	60	į S
Number born live	10.15	11.22	11.17	12.03	3.46	8	05	£ &
*Sows were removed for injur	ed for injury, no estrus by day 35, or age.	day 35, or	ige.					3

In conclusion, the results establish that feeding carnitine supplemented diets to sows during the gestation period only has the most beneficial effect on increasing pork productivity primarily by increasing litter and pig birth weights, and litter and pig wean weights. Some beneficial results were observed when carnitine was fed during both gestation and lactation periods. However, feeding carnitine during the lactation period only was least beneficial.

Having described this invention and its benefits in detail above, it will be apparent that a skilled practitioner can make modifications and changes of the invention without departing from the scope or spirit of the claims which follow.

2

7.

days during the first sixty days of gestation.

What is claimed is:

A method for supplementing sow diets with carnitine comprising: 1 1. feeding an effective amount of L-carnitine or a salt thereof to a sow during the gestation 2 3 period from mating. The method of claim 1, wherein said carnitine is fed from 1 2. approximately mating to parturition in the amount from approximately 9 to approximately 2 3 14,000 mg per day per sow. 1 The method of claim 1, wherein said carnitine is fed from mating in 3. the amount from approximately 9 to approximately 14,000 mg per day per sow, and 2 throughout all or part of period of lactation in the amount from approximately 20 to 3 4 approximately 34,000 mg per day per sow. 1 4. A method for supplementing sow diets with carnitine comprising: feeding from approximately 9 to approximately 14,000 mg L-carnitine or a salt thereof per 2 day per sow during the gestation period from mating, but not during lactation. 3 1 5. The method of claim 4, wherein said carnitine is fed from 2 approximately mating to parturition. 1 6. The method of claim 4, wherein said carnitine is fed for at least five 2 days during the first sixty days of gestation.

The method of claim 4, wherein said carnitine is fed for at least ten

1 8. The method of claim 4, wherein said carnitine is fed for at least five 2 days during the first ninety days of gestation. The method of claim 4, wherein said carnitine is fed for at least ten 1 9. days during the first ninety days of gestation. 2 1 10. The method of claim 4, wherein said carnitine is fed in the amount 2 of from approximately 9 to approximately 550 mg per day per sow. 1 11. A method for supplementing sow diets with carnitine comprising: feeding a diet formulation comprising from about 5 to about 5,000 ppm L-carnitine or a 2 3 salt thereof to a sow during the gestation period from mating. 1 12. The method of claim 11, wherein said diet formulation is fed from 2 approximately mating to parturition. 1 13. The method of claim 11, wherein said diet formulation is fed from 2 mating and throughout all or part of period of lactation. 1 14. The method of claim 11, wherein said diet formulation comprises 2 from about 50 to about 200 ppm of carnitine. 1 15. The method of claim 11, wherein the diet comprises from about 2 12% to about 30% by weight of crude protein. 1 16. A method for supplementing sow diets with carnitine comprising: feeding a diet formulation comprising from about 5 to about 5,000 ppm L-carnitine or a 2 salt thereof to a sow during the gestation period from mating, but not during lactation. 3

1 17. The method of claim 16, wherein said diet formulation is fed from 2 approximately mating to parturition. The method of claim 16, wherein said diet formulation is fed for at 1 18. 2 least five days during the first sixty days of gestation. 1 The method of claim 16, wherein said diet formulation is fed for at 19. 2 least ten days during the first sixty days of gestation. 1 20. The method of claim 16, wherein said diet formulation is fed for at 2 least five days during the first ninety days of gestation. 1 21. The method of claim 16, wherein said diet formulation is fed for at 2 least ten days during the first ninety days of gestation. 1 22. The method of claim 16, wherein said diet formulation comprises 2 from about 50 to about 200 ppm of carnitine. 1 23. The method of claim 16, wherein said diet formulation comprises 2 from about 12% to about 30% by weight of crude protein.

				•	•	
		·°				•
						•
•		•				
					÷	
₹						
			×			
	ī					
	4 1					
			*			
4,						,
				•		

INTERNATIONAL SEARCH REPORT

Inter onal Application No PCT/US 97/22215

A CLAS	SIFICATION OF SUBJECT MATTER		
ÎPC 6	A23K1/16 A23K1/18 A61K	31/205	
According	to International Patent Classification(IPC) or to both national cl	assification and IPC	
B. FIELD	S SEARCHED		
Minimum of IPC 6	documentation searched (classification system followed by class $A23K-A61K$	sification symbols)	
Document	ation searched other than minimum documentation to the extent	that such documents are included in the fields se	arched
Electronic,	data base consulted during the international search (name of da	ata base and, where practical, search terms used)
C. DOCUM	MENTS CONSIDERED TO BE RELEVANT		
Category '	Citation of document, with indication, where appropriate, of the	ne relevant passages	Relevant to claim No.
Ρ,Χ	R.E. MUSSER ET AL.: "Added L- fed during gestating increases weight of pigs"	carnitine birth	1,4,11, 14,16,22
	JOURNAL OF ANIMAL SCIENCE, vol. 75, no. Suppl. 1, 1997, U page 199 XP002061792 see Abstract 250	ıs,	•
A	D.C. HONEYFIELD ET AL.: "Eval energy sources with and withou in newborn pig heart and liver JOURNAL OF NUTRITION, vol. 121, no. 7, 1991, US, pages 1117-1122, XP002061793 see the whole document	t carnitine	1
		-/	
χ Furth	er documents are listed in the continuation of box C.	χ Patent family members are listed in	annex.
'A" documer conside 'E" earlier do filing da		"T" later document published after the interm or priority date and not in conflict with the cited to understand the principle or the invention "X" document of particular relevance; the cla	ne application but bry underlying the imed towartion
which is citation O" document other m	nt which may throw doubts on priority claim(s) or s cited to establish the publication date of another or other special reason (as specified) int referring to an oral disclosure, use, exhibition or seans at published prior to the international filing date but	cannot be considered novel or cannot be involve an inventive step when the doc. "Y" document of particular relevance; the claca cannot be considered to involve an invedocument is combined with one or more ments, such combination being obvious in the art.	iment is taken alone imed invention ntive step when the other such docu-
later tha	an the priority date claimed clual completion of theinternational search	"&" document member of the same patent (a	
	April 1998	Date of mailing of the international search	h report
lame and ma	alling address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,	Authonzed officer	
	Fax: (+31-70) 340-3016	Dekeirel, M]

1

Inter phal Application No PCT/US 97/22215

		PCT/US 97/22215
	nation) DOCUMENTS CONSIDERED TO BE RELEVANT	
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	M.T. COFFEY ET AL.: "Carnitine status and lipid utilization in neonatal piglets fed diets low in carnitine" JOURNAL OF NUTRITION, vol. 121, no. 7, 1991, US, pages 1047-1053, XP002061794 cited in the application see the whole document	1
A	J. KERNER ET AL.: "A study of the acylcarnitine content of sows' colostrum, milk and newborn piglet tissues: demonstration of high amounts of isovaleryl-carnitine in colostrum and milk" JOURNAL OF NUTRITION, vol. 114, no. 5, 1984, US, pages 854-861, XP002061795 see the whole document	1
	EP 0 680 945 A (OMEARA PTY LTD) 8 November 1995 see page 7, line 17 - line 21 see claims 1,8,11	1
	EP 0 535 440 A (SIGMA TAU IND FARMACEUTI) 7 April 1993 see the whole document	

INTERNATIONAL SEARCH REPORT .dormation on patent family members

Inter onal Application No PCT/US 97/22215

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0680945 A	08-11-95	AU 1780395 A ZA 9504224 A JP 8333313 A	09-11-95 22-01-96 17-12-96
EP 0535440 A	07-04-93	IT 1249706 B JP 5194206 A ZA 9207100 A	09-03-95 03-08-93 31-03-93

			. 4 .	
		(*)		, já
				,
	48			
A.				
	•*·			
. **				
			•	
		•		
	į.	7) 2
	Ý		•	7.